CONCEPT

An analysis of the incidence of myocardial metastasis from solid cancers

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Abstract

Metastasis to the heart is compared with that to other target sites in terms of incidence, tissue susceptibility, and cancer cell injury within the microcirculation. At necropsy the myocardium is the sixth most common site for arterial metastasis among eight target organs in ten different types of disseminated primary cancer. However, the metastatic efficiency index (incidence/blood flow) indicates that the myocardium is no less susceptible to metastatis per unit of cancer cells delivered than most other sites examined. The analyses also indicate that cancer cells causing myocardial metastasis are mainly derived from metastatic or primary tumours in the lungs. Experiments on laboratory animals suggest that the failure to develop myocardial metastasis in 80 to 98% of patients with metastatic cancer is at least partially due to lethal, deformation-associated, mechanical damage inflicted on cancer cells trapped within the myocardial microvasculature.

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The aims of this paper are first to record and comment on the incidence of cardiac metastasis seen at necropsy in cases with a history of different, metastasing "solid" cancers. Second, this incidence will be compared with that of other target organs. Third, the susceptibility of the myocardium to haematogenous metastasis will be compared with that of other organs by use of metastatic efficiency indices. Finally, some mechanisms influencing the development of haematogenous metastasis in the myocardium will be discussed in the light of laboratory experiments.

Incidence of myocardial metastasis

Interest in myocardial metastasis has been limited because it is not usually diagnosed during life and when it is it is usually during the terminal phases of cancer. It is a truism that the actual numbers of cases detected are highest for the most common cancers; this is sometimes confused with the real incidence in each different type of primary cancer. In addition, in each type of primary cancer not only must a distinction be made between the incidence in patients with metastatic and non-metastatic disease but also attention must be given to the occurrence of metastatic "cascades", as discussed later.

True embolic metastasis to the myocardium occurs via the coronary arteries and, much less commonly, by implantation in the right cardiac chambers of cancer fragments carried in the venae cavae. In the present context it is important to discriminate between these lesions and non-metastatic extension from contiguous tumours, particularly of the bronchus and oesophagus and in the mediastinal lymph nodes.[1] According to Willis lymphatic permeation from the epi and peri cardial lymphatic vessels is not rare and the less common invasion of the vena cava and pulmonary veins extends no further than the atria by the time of death. The analyses made here will be confined to true embolic metastasis of the myocardium via the coronary arteries, with the less common routes or lesions excluded or ignored.

Table 1 Incidence (%) of metastasis from primary carcinomas in 10 target organs

	Percentage target organ involvement							
Metastatic primary cancers	*Kidneys*	*Brain*	*Bone*	*SM*	*Skin*	*Heart*	*Thyroid*	*Adrenals*
Breast	17·0	22·8	61·8	15·5	19·5	10·3	24·0	31·2
Colorectum	13·0	11·0	27·0	3·0	5·0	2·0	4·0	31·0
Oesophagus	36·8	13·2	28·9	7·9	0	13·4*	13·2	42·1
Kidney	21·2	19·4	10·2	3·5	5·3	14·0	10·6	20·1
"Lung"	22·5	42·9	32·5	—	<1·0	7·5	2·5	35·6
Lung/SCC	16·0	37·3	56·2	—	—	17·2*	4·6	35·0
Ovary	6·3	2·9	11·3	—	5·2	5·2	14·7	20·4
Pancreas	18·9	8·1	47·0	9·2	3·8	8·1	3·2	44·8
Prostate	14·2	2·1	66·8	—	2·6	3·0	2·1	17·3
Stomach	13·0	6·9	16·8	5·3	3·8	5·6*	2·3	3·5

SCC, small cell carcinoma; SM, skeletal muscle.
*Incidence of cardiac metastasis reference 2; sources for other sites given in reference 5.

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Table 1 shows the incidence of metastatis in the myocardium and other target organs from 10 common primary cancers when selective criteria indicated above are used. In addition, the incidence of myocardial metastasis in the cervix uteri, urinary bladder, and uterus was 6·1%, 11·8%, and 16·7% respectively.[2] These incidences are conservative because false negative reports are likely as a result of sampling and detection errors during necropsy[3] and subsequent standard histopathological examination of tissues.[4]

For carcinomas of the oesophagus, bronchus (small cell carcinoma), and stomach data from the Klatt and Heitz[2] series were used because previously collected data on target sites for these primary cancers did not include the incidence of cardiac metastasis. The inclusion of data from this series was justified because the incidences of cardiac metastasis reported by Klatt and Heitz in primary metastatic cancers of the breast (12·5%), colorectum (3·1%), kidney (11·5%), and ovary (7·7%) were very close to the corresponding values obtained from other sources[5] and given in table 1.

Data on the 13 specified types of primary cancer were available for up to eight target sites—that is for a total of 99 of a possible maximum of 104. For the eight tabulated sites cardiac metastases had the sixth mean highest incidence (table 1). Among those primary cancers with cardiac metastases, the highest incidences occurred in cases with a history of small cell carcinoma of the lung (17·2%) and carcinomas of the uterus (16·7%), kidney (14%), and oesophagus (13·4%). The high incidence in uterine and kidney carcinoma could not have been the result of direct extension from these primary lesions. Conversely, the similar incidences at these sites and in the lung and oesophagus, suggests that extension from these latter primary sites played a minor role in the genesis of cardiac metastasis, as recorded here.

Cardiac metastasis was present in 9·3% of approximately 2500 cases with a history of metastatic primary cancers. This mean value compares with that of 14·9% (range 7–26%) in the 1934 cases collated previously,[6] which also showed that in the absence of detectable metastases elsewhere, particularly in the lungs, myocardial metastatis was rare. For example, necropsies performed in the Roswell Park Cancer Institute from 1959 to 1982, on 9501 patients with histories of primary cancers (excluding the lung) showed a 19% incidence of cardiac metastasis in 4330 patients with lung metastasis; however, among 5109 patients without detected lung metastases only 2·7% had cardiac metastasis.[6] This can be accounted for by traffic of cancer cells to the myocardium. Only a small proportion of cancer cells shed by primary lesions are expected to survive passage through the microcirculation of the lungs where most are trapped and, of these, most are killed.[7,8] In the case of cancer cells entering the portal system from colorectal carcinomas for example, even fewer will survive direct passage through the microvasculature of both the liver and lungs en route to the myocardium, where most of the delivered cells are also killed. This suggestion is supported by the low (2%) incidence of myocardial metastasis in colorectal carcinoma. One mechanism for rapid cancer cell death within the microvasculature is discussed below (section 3).

In view of the massive intravascular death of cancer cells the commonest way for large numbers of tumourigenic cancer cells to enter the myocardium via the coronary arteries is directly from lung tumours (primary and metastatic lesions) via the pulmonary veins. This at least partially accounts for the higher incidence of myocardial metastasis in patients with pulmonary metastasis over those without them and for the higher incidence in patients with primary small cell carcinomas of the lungs. This process of metachronous seeding by metastasis from metastases (metastatic "cascades") was shown in various cancers by Bross *et al*[9] and in colonic,[10] renal,[11] and pancreatic[12] carcinomas.

Metastatic patterns and metastatic efficiency indices

Two non-exclusive explanations have been offered for the specific patterns of target organ involvement seen with different primary cancers. In the first[13] the dominant factor is considered to be the numbers of cancer cells

Table 2 Metastatic efficiency indices (MEI): percentage of target organ involvement (from table 1) divided by target organ blood flow

	Target organs							
	Blood flow (ml/min)							
Metastatic primary cancer	*Kidneys (1000)*	*Brain (750)*	*Bone (600)*	*SM (560)*	*Skin (400)*	*Heart (240)*	*Thyroid (100)*	*Adrenals (90)*
Breast	0·017	0·030	0·103	0·028	0·049	0·043	0·240	0·347
Colorectum	0·013	0·015	0·045	0·005	0·013	0·008	0·040	0·344
Oesopahgus	0·037	0·018	0·048	0·014	0	0·056	0·132	0·468
Kidney	0·042	0·026	0·017	0·006	0·010	0·058	0·110	0·447
"Lungs"	0·023	0·057	0·054	—	0·001	0·031	0·025	0·396
Lungs/SCC	0·016	0·050	0·094	—	0·001	0·072	0·046	0·389
Ovary	0·006	0·004	0·019	—	0·013	0·022	0·147	0·229
Pancreas	0·019	0·011	0·078	0·016	0·010	0·034	0·032	0·487
Prostate	0·014	0·003	0·111	—	0·007	0·013	0·021	0·192
Stomach	0·013	0·009	0·028	0·009	0·010	0·023	0·023	0·039

*Red bone marrow. Numbers in parentheses are organ blood flows in ml/min.

delivered in the bloodstream to the different target sites. Thus the lungs are the most common early sites for primary cancers with initial drainage into systemic veins and the liver is the most common for those draining into the portal system.

In mice the delivery of cancer cells to different target organs after they had been injected into the left ventricular cavity correlated closely ($r = 0.99$) with target organ blood flow.[14] In humans delivery of cancer cells is also expected to correlate with blood flow. I have collated information from various sources[15] and table 2 includes information on myocardial blood flow.[16 17]

A comparison of the incidence of metastases in the different target organs (table 1) with their blood flow (table 2) does not show a correlation. In addition, only in the case of colorectal carcinoma does the incidence of cardiac metastasis lie between the values for the skin and thyroid, which have blood flows respectively above and below that in the myocardium. Therefore, although the delivery of cancer cells to target organs is an absolute requirement for metastasis, it does not account for the incidence patterns recorded here. However, the only data available on incidence relate only to whether or not evidence of metastasis was detected in any site, not how many metastases were present.

The disparity between cancer cell delivery and blood flow is addressed by the "seed-and-soil" hypothesis of Paget.[18] In this, differential interactions between different sites ("soils") and different types of cancer cells ("seeds") are thought to determine the relative susceptibilities of target sites to metastasis.

To discriminate between the differential delivery of cancer cells and differential interactions with target sites after delivery a semi-quantitative metastatic efficiency index (MEI) (percentage incidence of organ involvement divided by organ blood flow (ml/min) was developed.[5] In the initial study of the involvement of eight different target sites by metastasis from 19 groups of primary cancers, the MEIs that could be calculated in 135 of 152 possible situations, fell into three decades. Most (65%) had values of 0·01–0·09, 20% had values of 0·1–0·9 (indicating a "friendly" microenvironment with a relatively high incidence of metastasis per unit number of delivered cancer cells), and in contrast 15% had MEIs of 0–0·009 (indicating a "hostile" environment with a relatively low incidence of metastasis per delivered unit).

Table 2 shows the MEIs calculated for 76 of 80 possible combinations of primary and target sites: 48 (63%) fell into the middle decade, which included all cases of cardiac metastasis. The mean (SEM) MEI for these lesions was 0·039 (0·006), including metastasis from primary cancers of the cervix uteri (0·025), bladder (0·049), and uterus (0·070). Therefore, although the incidence of myocardial metastasis was sixth in the hierarchy of the eight target sites reported, on the basis of MEI only 16 (20%) of 76 of other sites fell into the higher susceptibility decade and, of these, most were in the adrenals and thyroid.

Death of cancer cells in the myocardial microcirculation

Among those patients dying with metastatic cancer in the present study, between 83 and 98% did not have cardiac metastases detectable at necropsy. Large numbers of cancer cells must have been delivered to the myocardium but most of them must have failed to grow into metastases. This is an example of metastatic inefficiency.[8]

Interactions of cancer cells with the microvasculature of target sites are thought to be important rate regulators of haematogenous metastasis.[19] Studies in laboratory animals[20] showed that most cancer cells delivered to the myocardium via the coronary arteries after left ventricular injection are killed within several minutes: virtually no cancer cells were detected on histochemical examinations, and sensitive myocardial bioassays indicated that between 80% and 95% of cells entering the myocardium were rapidly killed. Cancer cell death was not due to the toxicity of the myocardium *per se*. Fewer cancer cells were killed when they were added to minced myocardium, which indicates that toxicity of the myocardium alone did not explain cancer cell killing.

One mechanism accounting for the destruction of cancer cells in the microvasculature of the heart and other target organs comes from considerations of cell geometry.[6 21] In vessels down to arteriolar diameter, circulating cancer cells tend to remain spherical. But when they enter vessels that have smaller diameters than they do they become cylindrical. Because a sphere has the smallest surface area of any body of equal volume, this transformation from sphere to cylinder must be associated with an increase in the surface area of the cancer cells. This increase can be apparent and be accomplished by non-lethal surface unfolding or, if unfolding is insufficient to meet the geometric demands, the increase may be real and accomplished by stretching of the surface membranes of the cancer cells. Biological membranes in general cannot be stretched to increase their surface areas by more than 4%, before the tension within them rises to the critical level for rupture, with consequent cell death. Intravascular cancer cell deformation with increases in surface area and death has been directly demonstrated by vital microscopy and has been shown to be the result of mechanically induced deformation.[22] Small cells with a high degree of membrane rugosity are expected to be most resistant to membrane damage induced by intravascular deformation. Thus erythrocytes and leukocytes, which are small and have membrane "excess", are more resistant than the generally larger and often less rugose cancer cells from solid tumours. Some leukaemia cells fall between these two extremes. It is therefore of interest that cardiac metastasis is more common in patients with lymphoreticular malignancies[23–25] than in those with solid tumours.

The myocardial capillaries would be expected to be especially lethal to cancer cells because of the external pressures acting on them during systole. The lethal effects of

additional pressure on cancer cells with partially unfolded surface membranes has been demonstrated in vitro.[26] Although measurement of intramyocardial pressure is technically difficult and interpretation is controversial,[27] it is generally agreed that systole causes pressure gradients across the myocardium, decreasing from endocardium to epicardium.[28] These pressures correspond to hoop tensions in the muscle fibres that are greater than 2×10^5 dyn/cm,[29] and although the details of mechanical coupling between the myocardium, capillaries, and cancer cells are not known, these tensions are four to five orders of magnitude higher than the critical tensions required to rupture cancer cell membranes.[20] The fact that the MEIs for the myocardium were in the middle decade, however, suggests that in some target organs other factors have similar numerical effects to those of myocardial contraction. Direct evidence that muscle contraction is associated with increased killing of cancer cells trapped in the microvasculature, comes from bioassays of cancer cells delivered to contracting, resting, and paralysed quadriceps muscles in mice[30]: also the MEIs for skeletal muscle (table 2) are in the middle and low decades.

In the face of the mechanical damage outlined above it is at first sight surprising that myocardial metastases develop at all: none the less, even an inefficient process will succeed if repeated often enough. One possible additional explanation is that metastases develop initially at the myocardial surfaces where compression is minimal; clumps of cancer cells are more likely than single cells to be arrested in superficial vessels, which have larger diameters than the deeper vessels. Subsequent invasion associated with histolysis from the metastasis/heart interface could then provide a pressure-relief mechanism for the subsequent successful invasion and growth of metastases into the myocardium. Some support for this suggestion comes from Klatt and Heitz's[2] observation that in 110 cases with cardiac metastasis, there were 100 surface lesions (83 epicardial and 17 endocardial) compared with 42 intramyocardial lesions.

It must be emphasised that deformation-induced, lethal damage of cancer cells in the microvasculature is only one of several rate regulators of metastasis.[8 19]

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